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Assessment of anthracycline-induced long-term cardiotoxicity in patients with hematological malignancies

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Abstract:

BACKGROUND: Anthracyclines are antibiotic antineoplastic drugs used in the treatment of various hematological and solid malignancies. They are well-known for their cardiotoxic side effects which are related to their cumulative dosages. Many investigations are used to detect such cardiotoxicity, the gold standard of which is the endomyocardial biopsy that has a limited use because it is an invasive procedure. The aims of this study were to explore the cardiotoxicity induced by anthracyclines in patients with hematological malignancies by using electrocardiography (ECG) and echocardiography and to determine relationship between the detected changes in ECG and echocardiography, with some demographic and clinical variables.

PATIENTS AND METHODS: A cross-sectional study of fifty patients was recruited at Al-Imamein Al-Kadhemein Medical City from March 2014 to January 2015. ECG and echocardiography were done to the patients to study several parameters such as ejection fraction (EF), diastolic dysfunction, QRS voltage, QRS duration, and corrected QT (QTc) both at baseline and reassessment. Reassessment was done after completing induction for leukemia patients and at mid-term reassessment for lymphoma patients.

RESULTS: ECG showed reduction in QRS voltage, increase in QRS duration, and increase in QTc, all of which showed statistical significance and may reflect the effect on the depolarization and repolarization on the myocardium. The echo study showed the development of systolic left ventricular (LV) dysfunction (EF <55%) in 12% of patients and a statistically significant reduction in the mean of EF of the study group. It also showed statistically significant development of new diastolic dysfunction. Statistically significant association between reduction of QRS voltage (>30% from baseline) with the development of LV dysfunction was also found.

CONCLUSIONS: Significant changes in QRS voltage, QRS duration, QTc, as well as the occurrence of LV systolic dysfunction and diastolic dysfunction were noted. The mean cumulative dose at which LV systolic dysfunction occurred was about 250 mg/m^2.

Keywords:

Anthracycline, cardiotoxicity, hematological malignancies

Introduction

Anthracyclines are antibiotic antineoplastic agents that were discovered in 1963 when a red fluorescent dye was isolated from fermentation of broth of the bacteria *Streptomyces peucetius.*

Anthracycline-induced cardiotoxicity is termed type I chemotherapy-induced cardiotoxicity which is characterized by the presence of free-radical formation.[1] These radicals may be responsible for lipid peroxidation and DNA breaks.[2]

Anthracycline's cardiac effects were initially categorized into two distinct forms: early and late toxicity.[3] Early cardiac

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manifestations of anthracycline administration probably represent the actual insult, which later progresses to overt cardiomyopathy. These manifestations may be sufficiently subtle as not to be considered a serious medical concern. The importance of the initial injury is usually underappreciated as it almost never requires treatment.[3]

The most common findings seen are electrocardiographic changes, usually in the form of repolarization changes involving the ST-segment and the T-wave, and dysrhythmia usually in the form of supraventricular or ventricular ectopics, which are seen often and are only rarely sustained or malignant.[4]

Early toxicity is more common in the elderly and is probably related to underlying and unrelated heart disease that exists in the aging population and the associated likelihood of increased oxidative stress. Early toxicity is also more common with large single doses of doxorubicin.[5]

Late toxicity is related to the cumulative doxorubicin dose, with the injury resulting from the death of myocytes. The more recent data from Swain *et al*. and MD Anderson Cancer Center suggest that doxorubicin is substantially more cardiotoxic than was originally believed.[6]

It was observed that the estimated cumulative percentage of congestive heart failure was 5% of patients at cumulative dose of 400 mg/m^2, 26% of patients at dose of 550 mg/m^2, and 48% of patients at dose of 700 mg/m^2.[6]

There is no sensitive or specific test that reliably predicts which patient might develop cardiac dysfunction after treatment with anthracycline.[7]

The noninvasive tests have suboptimal predictive value that is manifestation of false-positive and false-negative results. At low cumulative dosages, when the likelihood of a decreased ejection fraction (EF) due to anthracycline is small, false-positive results may exceed the incidence of true-positive results. Noninvasive testing can result in the recognition or confirmation of early or subclinical abnormalities in selected patients. Two-dimensional (2D) echocardiography is the most widely available method for monitoring left ventricular ejection fraction. Advantages include portability and capability of assessing other measures of myocardial dysfunction as well as other cardiac lesions (such as valve disease). Measurement of resting global left ventricular (LV) function using either first pass or equilibrium multigated blood pool imaging (MUGA (multigated acquisition scan) scan) is an established technique for monitoring anthracycline cardiotoxicity. However, it is used less often than echocardiography. Conduction abnormalities are also a nonspecific finding; they are a manifestation of congestive heart failure but may be related to other factors as well; they are also not helpful as a predictive parameter for following up patients receiving doxorubicin.[8]

All patients should undergo a baseline measurement of EF using echocardiography or a nuclear technique. The baseline results are useful for later comparisons and identify patients with cardiac risk factors and thus require closer monitoring. Patients with normal systolic function and no risk factors will usually tolerate 550 mg/m^2 of doxorubicin or the maximum recommended cumulative dose of other anthracyclines. Toxicity at cumulative doses below 2/3 of the maximal recommended dosage (300 mg/m^2 in the case of doxorubicin) is unusual. In the cumulative dose range from 2/3 to the maximally recommended dose (300–550 mg/m^2 for doxorubicin), patients should be evaluated by obtaining a clinical history and follow-up echocardiogram, either at that time of or approximately 3 months after therapy.[8]

Aim of the study

1. To explore the cardiotoxicity induced by anthracyclines in patients with hematological malignancies using electrocardiography (ECG) and echocardiography as simple noninvasive techniques
2. To determine the presence of any association between the detected changes in ECG and echocardiography, with some demographic and clinical variables.

Patients and Methods

Study design

This is a cross-sectional study.

Study setting

Hematology ward at Al-Imamein Al-Kadhemein Medical City from March 2014 to January 2015.

Inclusion criteria

1. Diagnosed with the following types of hematological malignancies: acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma (NHL)
2. They received protocol of chemotherapy containing anthracyclines according to their condition [Table 1]
3. All patients had EF of 55% or more by echocardiography at baseline assessment
4. Verbal consent was taken from all patients regarding the study
5. Patients receiving drugs that prolong QT were excluded from the study.

Methods

ECG and echocardiography were done for all patients

Table 1: Chemotherapy protocols used in the treatment of the study group

Disease	Protocol	Comment
ALL	UKALL XII[10]	-
ALL	Hyper-CVAD[11]	Complex protocol involving the use of cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine
AML	DA 3 + 7[12]	Cytarabine (7 days) and daunorubicin (3 days)
AML-M3 (promyelocytic leukemia)	ATRA + doxorubicin (ADM)[12]	ATRA + 4 doses of doxorubicin on each other day
HD	ABVD[13]	ADM, bleomycin, vinblastine, and dacarbazine
NHL	RCHOP[14]	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

AML=Acute myeloid leukemia, ALL=Acute lymphocytic leukemia, NHL=Non-Hodgkin's lymphoma, HD=Hodgkin's disease, ATRA=All trans retnoic acid, ADM=adriamycin = doxorubicin

Table 2: Anthracycline used in treatment of the study group

Anthracycline	Mean±SD (mg/m²)	Minimum (mg/m²)	Maximum (mg/m²)
Doxorubicin	204.7±91.16	100	450
Daunorubicin	244.18±76.1	180	480

SD=Standard deviation

at baseline before starting chemotherapy. They were repeated at the time of clinical reassessment. Reassessment was done after completing the induction for leukemia patients and at mid-term reassessment for lymphoma patients. Reassessment was also done whenever there was a cardiovascular concern.

Corrected QT (QTc) was obtained directly from the device. ST-T changes were identified if ST depression or T-wave changes were noted. QRS voltage was calculated as the voltage of the net number of small squares in the vertical length of lead II (R wave–S wave). QRS duration was measured directly by the device.[9] The patients were treated with various chemotherapy protocols according to the type of hematologic malignancy [Table 1], some of ALL (acute lymphocytic leukemia) patients were treated with protocol of UKALL XII,[10] other ALL patients were treated with Hyper CVAD protocol,[11] AML (acute myeloid leukemia) patients were treated with daunorubicin+cytarabine protocol,[12] M3 subtype of AML was treated with all trans retinoic acid ATRA + doxorubicin,[12] Hodgkin disease was treated with ABVD protocol,[13] Non hodgkin lymphoma patients were treated with RCHOP protocol.[14]

Statistical analysis

The statistical analysis was done using IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY, IBM Corp).

Demographic and clinical categorical characteristics were simply present in frequency; Chi-square test was used to compare the qualitative variables; and parametric tests such as *t*-test (paired or unpaired) and ANOVA were used for quantitative variables.

Results

Demographic criteria

Fifty patients were included in this study. Twenty-three patients (46%) were males and 27 patients (54%) were females.

The mean (standard deviation [SD]) age of the patients included in this study was 35.4 (17.1) years, with no significant difference between the age means of both sexes, $P > 0.05$.

Diagnosis

Acute myeloid leukemia was the diagnosis in 14 patients (28%), acute lymphoblastic leukemia was the diagnosis in 13 patients (26%), NHL in 13 patients (26%), and Hodgkin's disease in 10 patients (20%).

Six patients (12%) had hypertension. Six patients (12%) had diabetes. One patient (2%) had renal disease. Two patients (4%) had hypothyroidism. Eight patients (16%) received radiotherapy during the course of treatment. Only four patients (8%) were smokers, four patients (8%) were exsmokers, and no one had alcohol consumption. All patients had no family history of hematological malignancy.

Twelve patients (24%) were treated by UKALL XII protocol. One patient (2%) was treated by hyper-CVAD. Ten patients (20%) were treated by 3 + 7 protocol, four patients (8%) were treated by ATRA + ADM, and ten patients (20%) were treated by ABVD. Thirteen patients (26%) were treated by R-CHOP.

The mean (SD) cumulative dose of doxorubicin was 204.7 (91.16) mg/m^2 and ranging between 100 and 450 mg/m^2.

The mean (SD) cumulative dose of daunorubicin was 244.18 (76.1) mg/m2 and ranging between 180 to 480 mg/m^2 [Table 2].

Assessment of cardiac toxicity

Clinical assessment

Having been treated with anthracyclines, one patient (2%)

Table 3: Electrocardiographic parameters at baseline and reassessment

ECG parameter	Baseline, mean±SD	Reassessment, mean±SD	Significance test	*P*
QRS voltage (mV)	0.618±0.087	0.572±0.097	*t*=3.581	0.001
QRS duration[a] (ms)	94.76±6.03	95.52±6.33	*t*=2.518	0.015
QTc interval[b] (ms)	398.6±12.9	411.12±15.9	*t*=6.8	<0.001
ST-T changes[c] (%)	1 (2)	4 (8)	χ^2=8.98	0.003

[a]No patient developed QRS duration >120 ms, [b]Only one patient had QTc >450 ms and had no electrolyte disturbances. (hypokalemia or hypocalcemia), [c]After exclusion of patients with electrolyte abnormalities. ECG=Electrocardiography, SD=Standard deviation, QTc=Corrected QT

who was previously asymptomatic developed orthopnea, basal crackles on chest auscultation, gallop rhythm, and leg edema. While another four patients (8%) developed exertional dyspnea and exercise intolerance.

Electrocardiography

Table 3 shows the changes in the studied ECG parameters and the significance of that change.

Echocardiography study

Table 4 shows the changes in the studied echocardiographic parameters and the significance of that change.

Association study

Association with treatment protocols

Majority of LV dysfunction was detected among patients treated by R-CHOP protocol comprising 5 patients 83.3% of those who developed LV dysfunction and the association was statistically significant [Table 5].

Association with the diagnosis

Cross tabulation of LV dysfunction with the diagnosis of the treated diseases showed high frequency of LV dysfunction among patients with NHL which was statistically significant ($P < 0.05$) [Table 6].

Treatment-related left ventricular dysfunction

Only patients treated with doxorubicin developed LV dysfunction, while those treated with daunorubicin did not develop LV dysfunction [Table 7].

Table 4: Changes in the studied echocardiographic parameters

Echo parameter	Baseline	Reassessment	*P*
Mean EF	64.98	62.02	<0.001
LV dysfunction (EF <55%)	0	6 (12)	<0.001
Diastolic dysfunction (%)	10 (20)	17 (34)	<0.001

EF=Ejection fraction, LV=Left ventricular

Table 5: Cross tabulation of left ventricular systolic dysfunction with treatment protocol of the study group

Treatment protocol	Left ventricular systolic dysfunction		
	Present	Absent	Total
R-CHOP	5	8	13
Hyper C-VAD	1	0	1
ABVD	0	10	10
UKALL XII	0	12	12
Doxorubicin + cytosar 3 + 7	0	10	10
ATRA + ADM	0	4	4
Total	6	44	39

χ^2=16.76, *P*=0.001. ATRA=All trans retnoic acid, ADM=adriamycin = doxorubicin, ABVD=A(adriamycin) B(bleomycin) V(vinblastine) D(dacarbazine), UKALL XII=United Kingdom acute lymphocytic leukemia no. 12 protocol for treatment, R-CHOP=R(rituximab) C(cyclophosphamide) H(hydroxydaunorubicin) O(oncovin) P(prednisolone), Hyper C-VAD=hyperfractionated cyclophosphamide V(vincristine) A(adriamycin) D(dexamethasone)

Table 6: Cross tabulation of left ventricular systolic dysfunction with diagnosis of the study group

Diagnosis	Left ventricular systolic dysfunction			*P* value
	Present	Absent	Total	
AML	0	14	14	Non significant
ALL	1	12	13	Non significant
HD	0	10	10	Non significant
NHL*	5	8	13	Significant (0.007)
Total	6	44	50	

χ^2=8.78, *P*=0.007. **P* value < 0.05 is significant. AML=Acute myeloid leukemia, ALL=Acute lymphocytic leukemia, NHL=Non-Hodgkin's lymphoma, HD=Hodgkin's disease

Table 7: Cross tabulation of left ventricular systolic dysfunction with the type of anthracycline used for the treatment of the study group

Anthracycline	LV dysfunction		
	Present	Absent	Total
Doxorubicin	6	23	29
Daunorubicin	0	21	21
Total	6	44	50

LV=Left ventricular

Discussion

In this study, there was no significant difference between both sexes regarding inclusion criteria, so that they were all suffering from hematological malignancies. There was no significant difference in mean (SD) of their ages either.

Patients were classified according to their diagnosis so that more than 1 type of hematological malignancies were included. Horacek *et al*.[15] in their study included leukemia patients, but they did not classify them. Uchikoba *et al*.[16] included hematological malignancies as well as solid tumors in their study. They also included a control group as their study was a case–control one, while this study is a prospective case series.

In the present study, different associated diseases were noticed. None of the patients showed

signs and symptoms of heart failure prior to chemotherapy, this was similar to Uchikoba *et al*.[16]

Treatment protocols used in the present study were UKALL XII, hyper-CVAD, doxorubicin + cytosar (3 + 7), ATRA + ADM, ABVD, and R-CHOP. The choice of the protocol was according to the guidelines of treatment of the included hematological malignancies. For this reason, the type of anthracycline and the cumulative dosages varied according to the type of malignancies and their treatment protocols. Horacek *et al*.[15] included the treatment protocols of acute leukemia. The mean cumulative dose of anthracyclines used in the present study did not differ much from those used in the study of Horacek *et al*.[15] They reported the mean (SD) cumulative dose to be 264.3 (117.5). In the present study, 1 (2%) patient developed symptoms and signs of congestive heart failure in the form of orthopnea, basal crackles on auscultation, gallop rhythm, and leg edema. Four patients (8%) developed increasing dyspnea on exertion and decreased exercise tolerance. The latter symptoms can also be explained by causes other than heart failure such as anemia or pulmonary diseases.

In a study of Limat *et al*.,[17] 10% of patients treated by R-CHOP developed clinical features of congestive heart failure.

On the other hand, there was a significant increase in QRS duration. However, none of the patients had QRS complex >120 ms. Nousianen *et al*. found no significant difference in QRS duration among patients with NHL treated by CHOP.[18]

QTc interval increased significantly from the baseline reading but with only one patient having QTc >450 ms. Horacek *et al*.[15] also reported a significant prolongation in QTc from 414.7 ± 16 to 430 ± 18.4 at the end of the study. In their study, five patients (19.2%) developed QTc >450 ms.

In the present study, significant new ST-T changes were found as compared to baseline ECG (after exclusion of patients with electrolyte abnormalities). Elme *et al*. reported ST-T changes in the ECGs of patients with left-sided breast cancer treated by doxorubicin.[19]

LV dysfunction developed in 6 (12%) with significant reduction of EF from the baseline. Statistically significant new diastolic dysfunction developed in 7 (14%) patients. Horacek *et al*.[15] reported LV dysfunction in 19.2% of patients at the end of their study. Their result also recorded diastolic dysfunction in 19.2% of patients.

Majority of patients in the present study who developed LV dysfunction had NHL. Nousianen *et al*.[18] found a significant reduction in EF in patients with NHL treated by anthracycline-containing protocol.

In the present study, the majority of patients who developed LV dysfunction were treated by R-CHOP protocol. In a study performed by Jurczak *et al*.[20] whereby patients with NHL lymphoma were treated by RCHOP protocol, RCHOP was associated with a significant reduction in EF. Limat *et al*.[17] found a significant occurrence of cardiovascular events (mostly due to congestive heart failure) in patients treated by CHOP. Coiffier *et al*.[21] found no significant difference in toxicity caused by R-CHOP as compared to CHOP. No further studies could be found to compare cardiotoxicity associated with R-CHOP treatment with other protocols.

In the present study, the occurrence of LV dysfunction was linked to the use of doxorubicin, while no patient treated with daunorubicin developed LV dysfunction. An explanation could be suggested for this difference; doxorubicin may be more cardiotoxic.

In the present study, the mean (SD) of cumulative dosages of doxorubicin in those patients who developed LV dysfunction was higher than the mean (SD) of those who did not develop LV dysfunction but with no statistical significance. However, LV dysfunction developed in patients who received doses as low as 150 mg/m^2. Nousiainen *et al*.[18] also found a significant decline in EF at low doses (about 200mg/m^2). Jurczak *et al*.[20] found death due to cardiovascular causes in patients who received doses not exceeding 200 mh/m^2.

In the present study, there was a significant association between the reduction of QRS voltage >30% from baseline and the development of LV dysfunction.

Shapira *et al*.[22] and Ali *et al*.[23] suggested that the reduction in QRS voltage >30% from baseline in limb leads can serve as a predictor of anthracycline-induced cardiomyopathy.

Horacek *et al*.[15] also found a significant correlation between the reduction in QRS voltage and LV systolic dysfunction.

Conclusions

1. The study showed significant changes in QRS voltage, QRS duration, and QTc associated with treatment with doxorubicin
2. The study showed a significant reduction in EF and development of LV systolic dysfunction and diastolic dysfunction among the studied patients
3. LV dysfunction occurred more in patients with NHL treated by R-CHOP protocol
4. There was a significant association between the reduction of QRS voltage (>30% from baseline) and the development of LV dysfunction

5. The cumulative dose of doxorubicin at which LV dysfunction occurred was about 250 mg/m^2.

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Conflicts of interest
There are no conflicts of interest.

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